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Brief Clinical Report

Extended Survival in a New Case of ter Haar Syndrome: Further Delineation of the Syndrome

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We present a boy followed from age 5–13 years who is the fifth reported case of ter Haar syndrome. This is a recently-named entity comprising congenital glaucoma, hypertelorism, congenital heart defects and kyphoscoliosis, skeletal dysplasia, and developmental delay. These patients were originally thought to have an autosomal-recessive form of Melnick-Needles syndrome, and were only identified as having a distinct syndrome with the report of the fourth case. Probable autosomal-recessive inheritance is based on consanguinity in 4 of 5 cases. Ocular, cardiac, and craniofacial findings distinguish ter Haar syndrome as a distinct entity. Our patient is the longest survivor at present, suggesting that there is heterogeneity in this syndrome or, alternatively, that aggressive therapy of the congenital heart defects has significant effect. Am. J. Med. Genet. 70:267–272, 1997.

KEY WORDS: ter Haar syndrome; congenital glaucoma; hypertelorism; congenital heart defects; congenital kyphosis; skeletal dysplasia

INTRODUCTION

Ter Haar et al. [1982] described 3 patients in one family with manifestations consistent with the diagnosis of Melnick-Needles syndrome. Two of the patients were males, suggesting the possibility of an autosomal-recessive form of Melnick-Needles syndrome. Melnick-Needles syndrome is a disorder of generalized bone dysplasia characterized by cortical irregularity, and shortness and bowing of the long bones with metaphyseal flare, usually inherited in an X-linked dominant pattern with lethality in hemizygous males [Donnenfeld et al., 1987]. Affected patients also have small facial bones with prominent eyes, full cheeks, and a small mandible with malalignment of teeth [Melnick and Needles, 1966]. The clinical diagnosis in the patients of ter Haar et al. [1982] was based on skeletal and craniofacial characteristics. The original 3 patients had the additional findings of congenital glaucoma and congenital heart defects, which were thought to be infrequent manifestations of Melnick-Needles syndrome. The cases of ter Haar et al. [1982] were part of the same extended family. Consanguinity was present in all 3 cases when the pedigree was expanded to include 10 generations, making recessive inheritance likely [Hamel et al., 1995]. Recently, Hamel et al. [1995] reported a boy with a similar phenotype in the same extended family as that studied by ter Haar et al. [1982]. It was proposed that this condition is distinct from Melnick-Needles syndrome and the eponym, ter Haar syndrome, was suggested. Manifestations of these patients are compared in Table I. The recessive inheritance pattern, congenital glaucoma, and congenital heart disease distinguish ter Haar syndrome as a unique entity.

We report on another individual with extended survival and anomalies similar to those of the patients of ter Haar et al. [1982] and Hamel et al. [1995]. We agree with the assertion that this represents a distinct syndrome, properly termed ter Haar syndrome.

CLINICAL REPORT

History

Our patient was the product of a 40-week pregnancy, born to a 20-year-old mother and a 19-year-old father, both of Puerto Rican heritage. The parents are first cousins once removed. Pregnancy was uneventful, except for nausea treated with an unknown medication. Maternal weight gain during pregnancy was 6.8 kg. Delivery was by cesarean section due to cephalopelvic

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TABLE I. Clinical Findings in Patients With ter Haar Syndrome

Patient no.	1[a]	2[a]	3[a]	4[b]	Our patient
Sex	M	M	F	M	M
Birth weight (g)	3,180	4,500	4,510	3,210	2,410
Craniofacial					
Prominent forehead	+	+	+	+	+
Brachycephaly		+	+	+	
Flat occiput	+	+	+	+	
Wide fontanel	+	+	+	+	+
Hypertelorism	+	+	+	+	+
Anteverted nostrils		+	+	+	
Micrognathia	+	+	+		+
Ocular					
Congenital Glaucoma	+			+	+
Large corneas	+			+	+
Prominent eyes	+	+	+	+	+
Skeletal					
Kyphosis	+			+	+
Short hands	+	+	+	+	
Flexion deformity				+	
Clubfeet	+		+	+	+
Prominent coccyx	+	+	+	+	
Skeletal dysplasia	+	+	+	+	+
Cardiac					
Double-outlet right ventricle		+		+	
Ventricular septal defect			+		
Mitral valve anomalies	+				+
Developmental					
Motor retardation	+	+		+	+
Developmental delay					+

[a]Patient reported by ter Haar et al. [1982].
[b]Patient reported by Hamel et al. [1995].

disproportion. Cry and respirations were recalled as being immediate, but Apgar scores are not available. Birth weight was 2,410 g (<3rd centile); length was 53 cm (90th centile); head circumference (OFC) at birth is not available. The baby was noted to have a "huge" anterior fontanelle measuring 10 cm, cleft of the soft palate, wide-set eyes, inguinal hernia, cryptorchidism, congenital glaucoma, and a thoracolumbar kyphosis.

Surgery for glaucoma was performed at age 2 weeks, and to date there have been 14 operations on both eyes. Mitral valve prolapse with mild mitral insufficiency and a prominent systolic click at the apex were noted in infancy. Bicuspid aortic valve was corrected surgically at age 4 years, leaving a residual cardiomyopathy requiring digoxin and an afterload reducer. Posterior spine fusion from T12 through L2 was performed at age 5 years for progressive thoracolumbar kyphosis. C1–C2 instability, detected at age 8 years, was treated with posterior spine fusion from occiput to C2, using an iliac graft.

Developmental status was evaluated at age 5 months when delays were noted, prompting an early intervention program. At age 4 years, language was at a 32-month level, self-help skills at 36 months, gross motor skills at 29–35 months, and fine motor skills scattered between 36–42 months. Developmental quotient was 73. Formal testing yielded a verbal IQ of 75, a performance IQ of 67, and a full-scale IQ of 68 on the Wechsler Preschool and Primary Scale of Intelligence. Intellectual functioning was assessed to be within the range of educable mental retardation.

Since age 7 years, height and weight have been <3rd centile, and OFC has remained between the 10–25th centiles.

Physical Manifestations

Our patient is a small youngster with unusual appearance (Figs. 1a,b and 2a,b). He has a normal neurocranial configuration with no palpable defects, frontal upsweep of hair pattern more marked on the left side with a single hair whorl near the vertex, low anterior hairline, normal eyebrows, very long, thick dark eyelashes, a slightly proptotic appearance, and asymmetry of palpebral fissures, the left fissure being twice the size of the right. Hypertelorism is dramatic: inner canthal distance is 3.5 cm (>97th centile), interpupillary distance 6.5 cm (>97th centile), and outer canthal distance 8.9 cm (90th centile). The irides are brown and the sclerae white. Megalocornea is present bilaterally with the left cornea measuring 12 mm, the right 13 mm. The corneas are clear. The nose is slightly short and broad at the level of the alae nasi with a short columella. He has a broad mouth (macrostomia) and tends to maintain an open-mouth habitus. There is midline furrow of the tongue. The lateral incisors are peg-shaped; 20 teeth are present with multiple diastemata. The palate is normal. Prominent and protruding ears were corrected surgically; they show simple folds and a slight cup-shape, with normal cartilage resilience.

Cervical spine motion is limited. There is no webbing or low nuchal hairline. The chest has a rounded anterior appearance, with no specific pectus deformity. The areolae are hypoplastic and hypopigmented. A grade

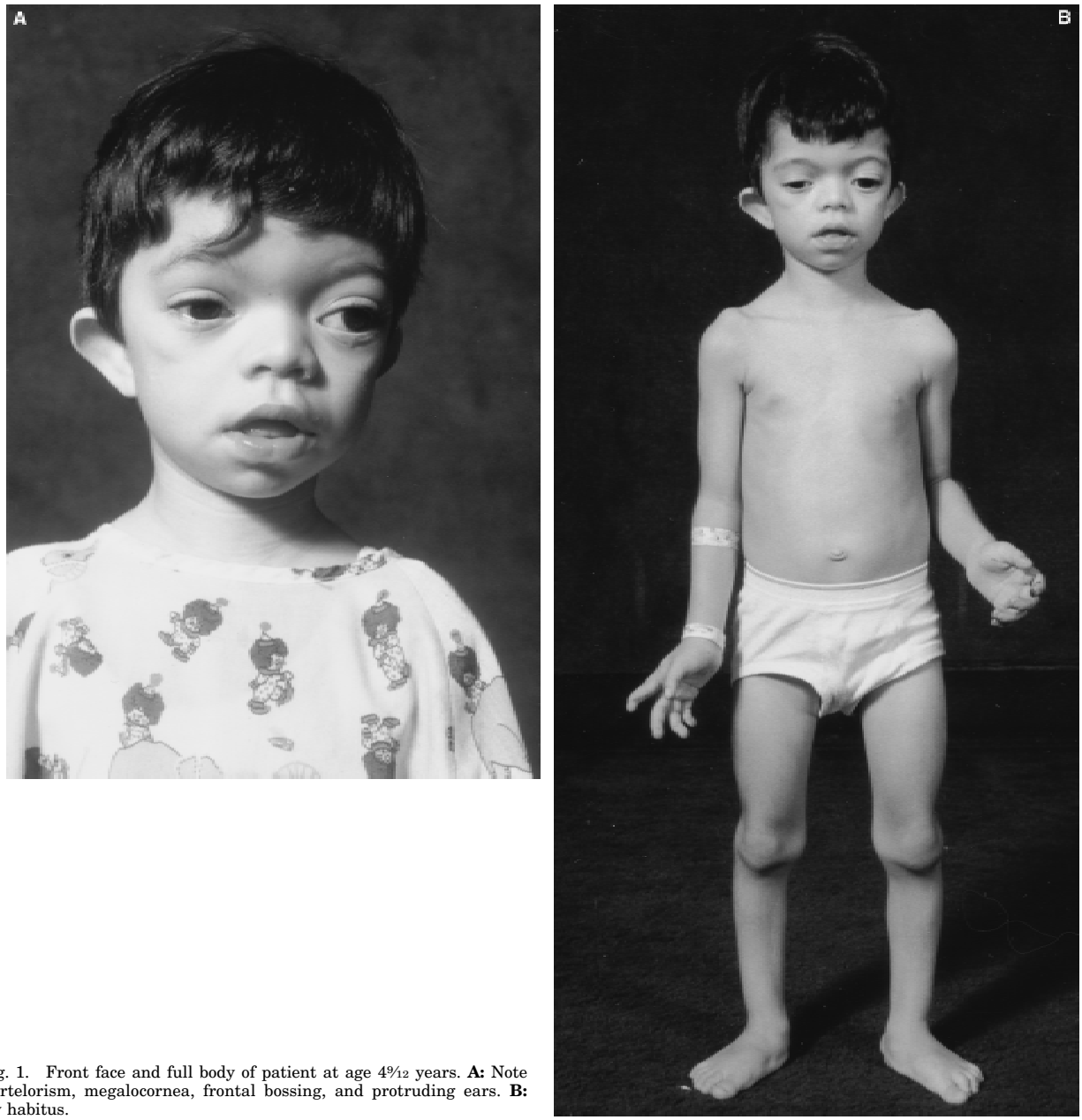

Fig. 1. Front face and full body of patient at age 4⁹⁄₁₂ years. **A:** Note hypertelorism, megalocornea, frontal bossing, and protruding ears. **B:** Body habitus.

V/VI systolic murmur was transmitted over the entire precordium and to the posterior lung fields. A thrill is palpable. There is no abdominal organomegaly. A 1-cm umbilical hernia is noted. At age 13 years, genital development is at Tanner stage I with normal penis and testes. A mild generalized hirsutism primarily affects the forearms and upper lateral arms. In addition, there is a patch of increased hair growth in the sacral area, with no palpable underlying bony defect. There are no significant pigmentary disturbances. Dermatoglyphics show five ulnar loops and five radial loops. The atd angle is approximately 40°. There are two transverse fifth-finger creases, and fused palmar flexion creases bilaterally.

The general appearance is that of a very thin, undernourished boy with little or no subcutaneous fat. The trunk is relatively short, with a sitting height of 61.7 cm and a standing height of 123 cm. There is increased diameter of the chest. All major joints are prominent because of poor muscle mass development. The genu recurvatum measures 10° bilaterally. Thoracolumbar kyphoscoliosis with a well-healed surgical scar is present. Both elbows lack 20° of pronation and supination; there are 10° of cubitus recurvatum. Hypermobile fingers allow unusual posturing with hyperextension of the proximal interphalangeal (PIP) joints, while the distal interphalangeal (DIP) joints are flexed. The thumbs are relatively long, and the proportionate fingers are cylindrical and nontapering. Bilateral pronated pes planus was noted. Ligamentous laxity at the

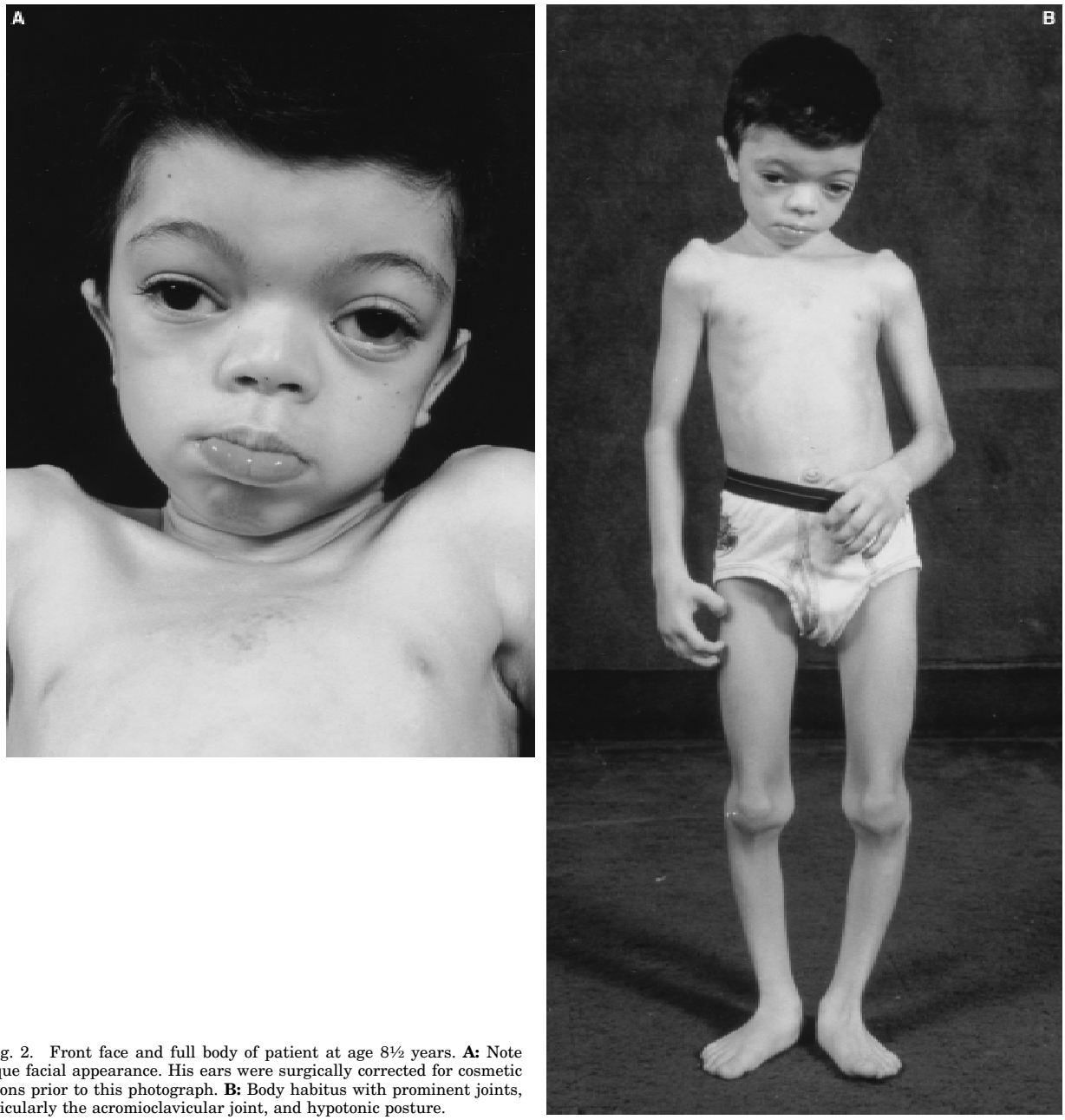

Fig. 2. Front face and full body of patient at age 8½ years. **A:** Note unique facial appearance. His ears were surgically corrected for cosmetic reasons prior to this photograph. **B:** Body habitus with prominent joints, particularly the acromioclavicular joint, and hypotonic posture.

knees is manifested by positive drawer signs and mild genu varum. Gait is wide-based. No focal neurological abnormality has been seen.

Laboratory and X-Ray Data

Chromosomes of lymphocytes and fibroblasts are normal. Results of routine blood count and serum chemistries were normal. T-waves in the electrocardiogram were inverted in lead III and flattened in the Augmented Voltage Foot (AVF), lead consistent with mitral valve prolapse. Echocardiography showed mitral insufficiency, mitral valve prolapse, and left atrial enlargement.

Radiography showed bilateral subluxation of the hips, with coxa valga and modeling deformity of the long bones (Fig. 3). There was no bowing or shortness of the long bones. The ribs do not have the ribbon-like quality seen in Melnick-Needles syndrome. There is double-curve scoliosis convex to the right 48° from T5–T10, and levoscoliosis of 34° from T10–L4. There is kyphoscoliosis centered at T12, measuring 20° at age 1 year and 43° at 5 years. A dysplastic odontoid was also noted. Generalized mild osteopenia was observed, especially in the vertebrae and hands (Fig. 4). Greulich

and Pyle bone age was estimated to be 7 years at a chronological age of 9 years. MRI of the patient's brain failed to show any abnormalities.

DISCUSSION

The combination of craniofacial, ocular, cardiac, skeletal, and developmental findings in the 3 patients of ter Haar et al. [1982], the patient of Hamel et al. [1995], and our present patient support the unique nature of ter Haar syndrome. Melnick-Needles syndrome was a diagnostic consideration for these individuals, but the abnormalities in ter Haar syndrome cover a broader spectrum, involving congenital heart defects and glaucoma. Autosomal-recessive inheritance of ter Haar syndrome seems most likely due to parental consanguinity in 4 of 5 cases. Four of 5 ter Haar syndrome patients reported thus far are males, making Melnick-Needles syndrome less likely due to its X-linked male lethal inheritance. There have been a few exceptions to lethality in males with Melnick-Needles syndrome, but this is exceedingly uncommon [Gorlin and Knier, 1982; Krajewska-Walasek et al., 1987].

Fig. 3. Radiograph of patient's lower limbs, showing modeling deformity of the long bones.

Fig. 4. Radiographs of patient's hands at age $\frac{8}{12}$ years, showing generalized osteopenia and bone age of 7 years.

Congenital heart defects seem to be a major finding in ter Haar syndrome, but are rarely associated with Melnick-Needles syndrome. The ter Haar patients have all had congenital heart defects with double-outlet right ventricle in 2, ventricular septal defect in 1, and mitral valve anomalies in 2 patients. In a series of 24 Melnick-Needles patients, there were no reports of congenital heart defects [von Oeyen et al., 1982]. There are reports of one early death due to congestive heart failure [Nyhan and Sakati, 1976] and of 2 children who died with severe respiratory compromise [Moadel and Bryk, 1977]. Congenital heart defects were reported in 1 of 4 patients in a series of males with lethal manifestations of Melnick-Needles syndrome [Donnenfeld et al., 1987].

Most of the patients of ter Haar et al. [1982] and Hamel et al. [1995] died in early childhood, attributed to the severity of their congenital heart disease. Our patient has had aggressive surgical and medical cardiac management. He is the oldest survivor at present, but as more individuals are identified, this may change. There may be heterogeneity within the syndrome affecting life expectancy. Alternatively, aggressive medical and surgical management of cardiac and pulmonary complications may have led to the extended survival in our patient.

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